

# ENOUGH IS NOT ENOUGH !!!!!



## ESLAM EID,MD

MANSOURA UNIVERSITY



Enjoy the Silence.

What is behind the number

When Enough Isn't Enough

Resuscitation of clinical sense

**Metabolic Syndrome &  
Type 2 Diabetes**

**It's a Nightmare!**



**Low-grade  
Inflammation**

**NASH**  
**Prothrombotic  
State**

**Hypertension**  
**Endothelial  
Dysfunction**

**Dyslipidemia**

**Hyperglycemia**

# The metabolic syndrome has several definitions

IDF <sup>1</sup>	NCEP-ATPIII <sup>2</sup> AHA/NHLBI <sup>3*</sup>	WHO <sup>4</sup>
Abdominal obesity, plus 2 of the following:	3 or more of the following:	Insulin resistance or diabetes, plus 2 of the following:
<ul style="list-style-type: none"> <li>Elevated triglycerides <math>\geq 150</math> mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality</li> <li>Low HDL-C Men <math>&lt;40</math> mg/dL (1.03 mmol/L), women <math>&lt;50</math> mg/dL (1.29 mmol/L), or specific treatment for this lipid abnormality</li> <li>High blood pressure SBP <math>\geq 130</math> or DBP <math>\geq 85</math> mm Hg or treatment of previously diagnosed hypertension</li> <li>Elevated blood glucose FPG <math>\geq 100</math> mg/dL (5.6 mmol/L) or previously diagnosed diabetes</li> </ul>	<ul style="list-style-type: none"> <li>Abdominal obesity Men <math>&gt;102</math> cm; women <math>&gt;88</math> cm</li> <li>Elevated triglycerides <math>\geq 150</math> mg/dL (1.7 mmol/L)</li> <li>Low HDL-C: Men <math>&lt;40</math> mg/dL (1.04 mmol/L), women <math>&lt;50</math> mg/dL (1.29 mmol/L)</li> <li>High blood pressure <math>\geq 130/85</math> mm Hg</li> <li>Elevated blood glucose <math>\geq 110</math> mg/dL (6.1 mmol/L)</li> </ul> <p>* Identical to the NCEP-ATP III definition with minor changes to the levels of each risk factor.</p>	<ul style="list-style-type: none"> <li>Obesity, defined as BMI <math>&gt;30</math> kg/m<sup>2</sup> and/or high waist: hip ratio (men <math>&gt;0.90</math>; women <math>&gt;0.85</math>)</li> <li>Elevated triglycerides <math>\geq 150</math> mg/dL (1.7 mmol/L)</li> <li>Low HDL-C Men <math>&lt;35</math> mg/dL (0.9 mmol/L), women <math>&lt;39</math> mg/dL (1.0 mmol/L)</li> <li>High blood pressure (<math>\geq 140/90</math> mm Hg)</li> <li>Microalbuminuria Urinary albumin excretion rate <math>\geq 20</math> g/min or albumin: creatinine ratio <math>\geq 30</math> mg/g</li> </ul>

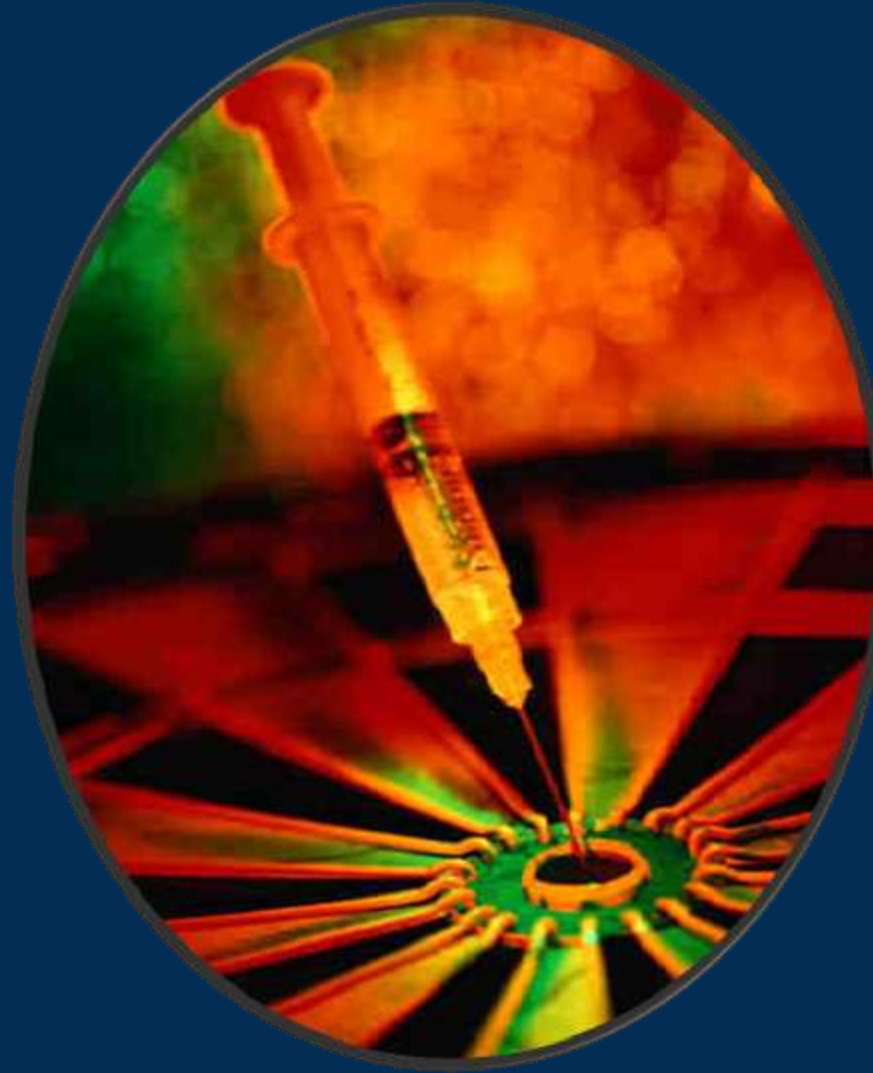
1. International Diabetes Federation. 2006. Available at: [http://www.idf.org/webdata/docs/MetS\\_def\\_update2006.pdf](http://www.idf.org/webdata/docs/MetS_def_update2006.pdf)

2. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002;106:3143-421.

3. Grundy SM, et al. Circulation. 2005;112:2735-52.

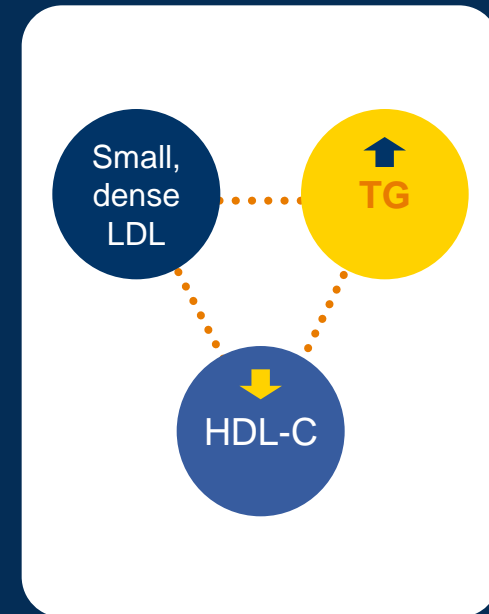
4. World Health Organization. 1999. Available at: [http://whqlibdoc.who.int/hq/1999/WHO\\_NCD\\_NCS\\_99.2.pdf](http://whqlibdoc.who.int/hq/1999/WHO_NCD_NCS_99.2.pdf)

# How to Obtain “proper” Control



# Atherogenic dyslipidaemia

- Patients with type 2 diabetes or metabolic syndrome have a typical atherogenic lipoprotein profile:
    - Elevated triglycerides
    - Reduced HDL-C
    - Increased small, dense LDL
    - Total LDL-C not significantly increased
  - These patients are at a particularly high risk for CHD
- Relative lipid levels in patients with atherogenic dyslipidaemia

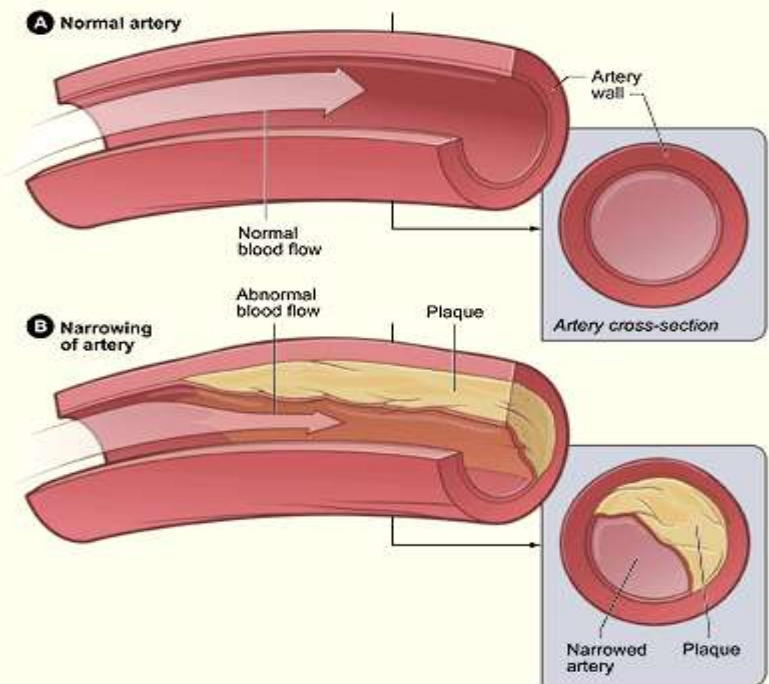


	LDL-C	HDL-C	TG
Relative level	↔	↓	↑



# What is atherosclerosis?

- Atherosclerosis is a disease in which plaque (fatty deposits) accumulates in medium- and large-sized arteries
- Depending on the type of atherosclerotic lesion, the plaque is composed of lipid, calcium, cells and/or matrix components, including minerals



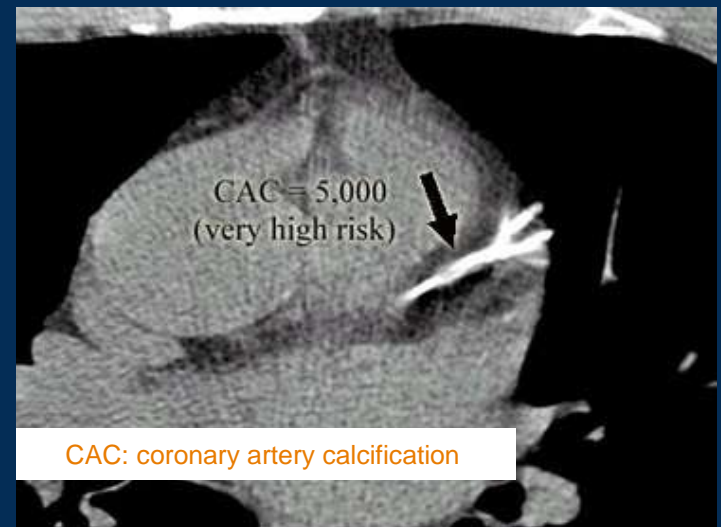
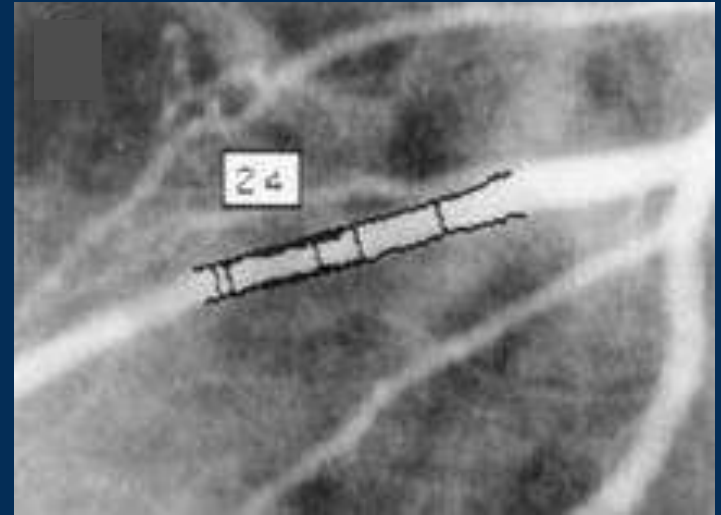
# What are the causes of atherosclerosis?

- Atherosclerosis is believed to begin with damage to the inner wall of the artery, leading to the build-up of fats and other substances and eventual plaque formation
- Causes of damage to the arterial wall and subsequent development of atherosclerosis include:
  - Physical stresses from turbulent blood flow (high blood pressure)
  - Inflammatory stresses caused by the immune system
  - Smoking
  - Diabetes
  - Elevated levels of cholesterol and triglycerides



# Numerous techniques exist for the detection of atherosclerosis

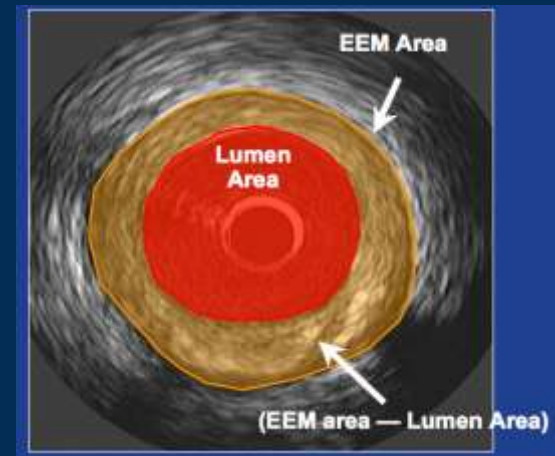
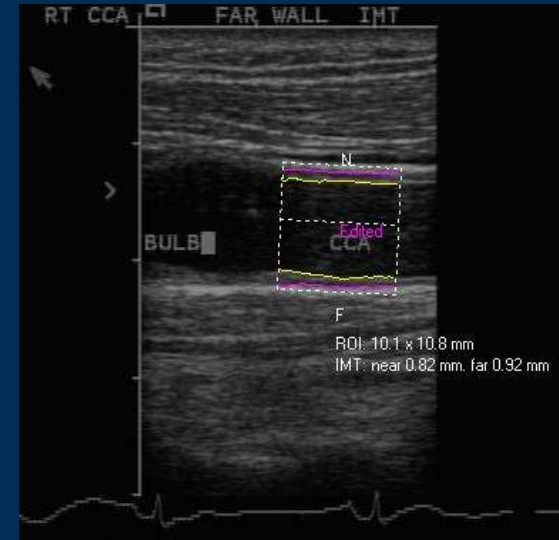
- Quantitative coronary angiography – visualises the lumen of coronary arteries and measures its diameter
- Coronary calcification score – detects calcification in arteries, a sign of atherosclerosis





# Numerous techniques exist for the detection of atherosclerosis

- Carotid ultrasound intima-media thickness (CIMT) – measures the thickness of the arterial wall, which is used as a surrogate marker for atherosclerosis
- Intravascular ultrasound (IVUS) – provides a cross-sectional view of the inside of coronary arteries



EEM: external elastic membrane

# Example of Significant Coronary Calcification from Multidetector CT (Siemens Sensation 64) scanner

ID: MESA4011988 Nam  
Date: 20050711 Time:

Current Lesion Info  
Pixels: 9 Peak HU: 236  
Volume: 12.62 Score: 8  
Mass: 2.18  
MeanHU: 175.89

-49 -66

38 23

192 151

183 205

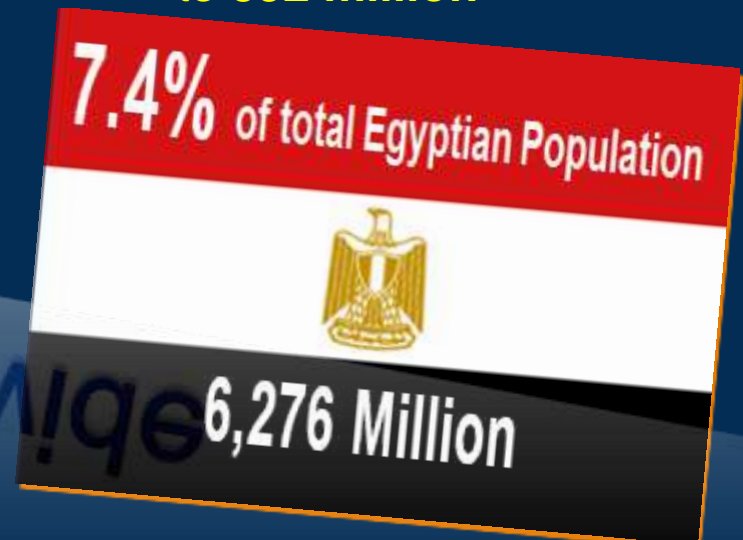
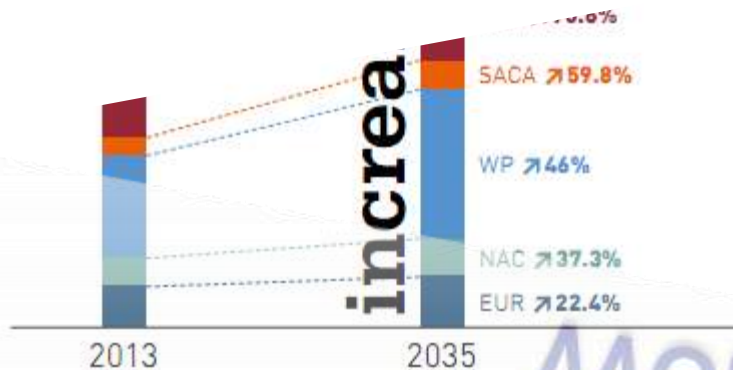
112 157

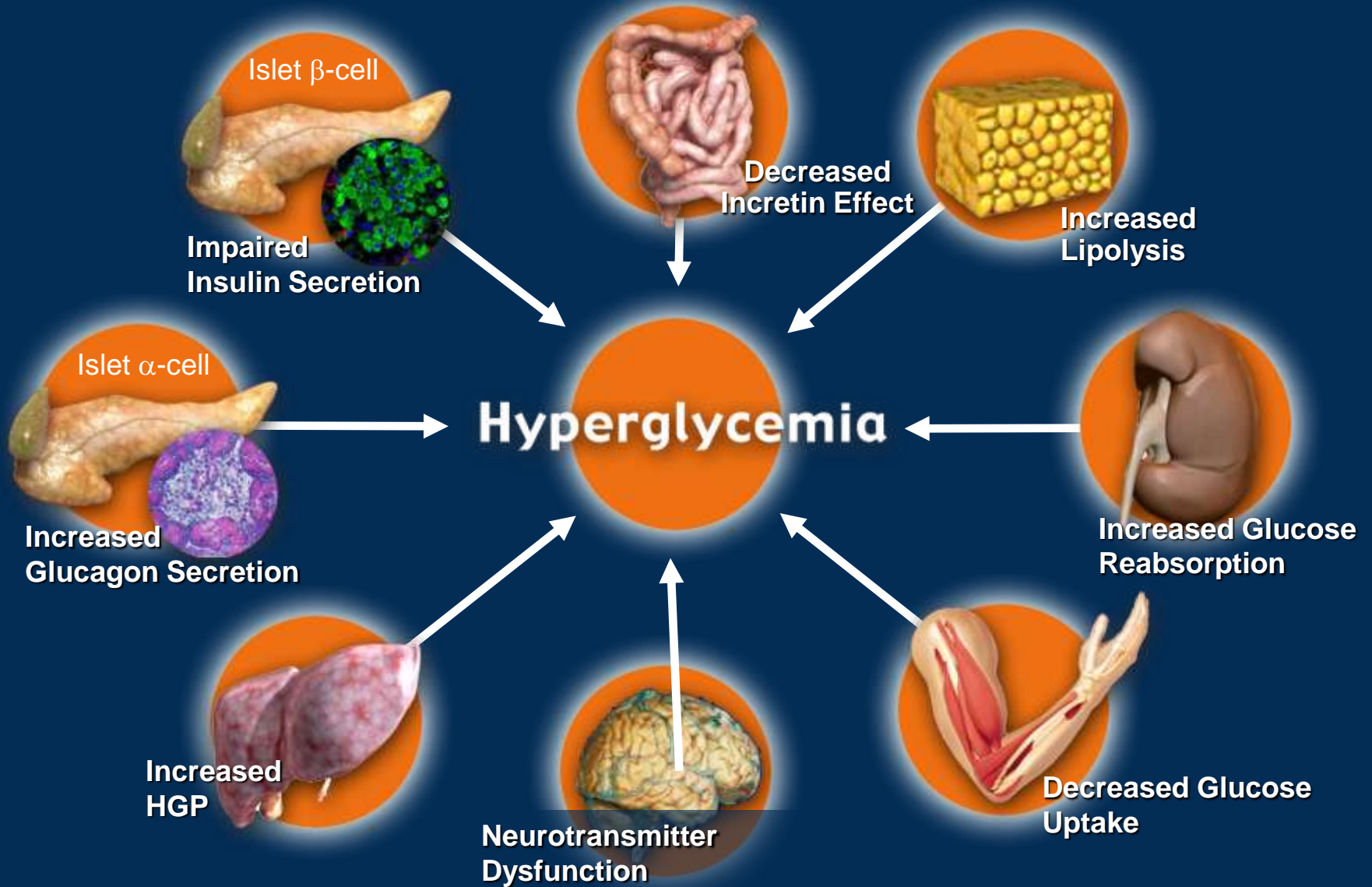
65 103

Diabetes is a huge and growing problem, and the costs to society are high and increasing

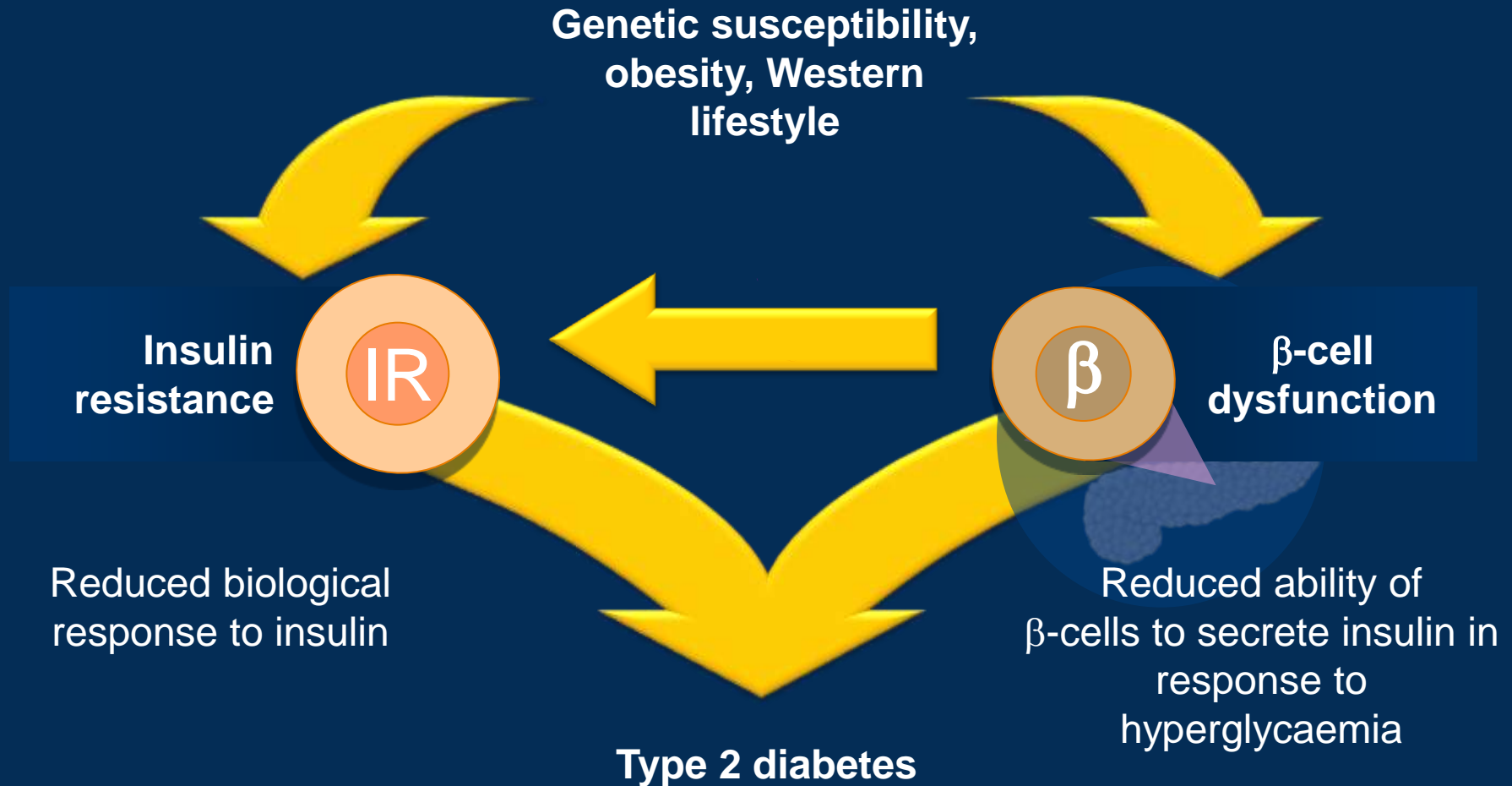
7.5% of Population  
Worldwide

By 2035, this number will rise to 592 million



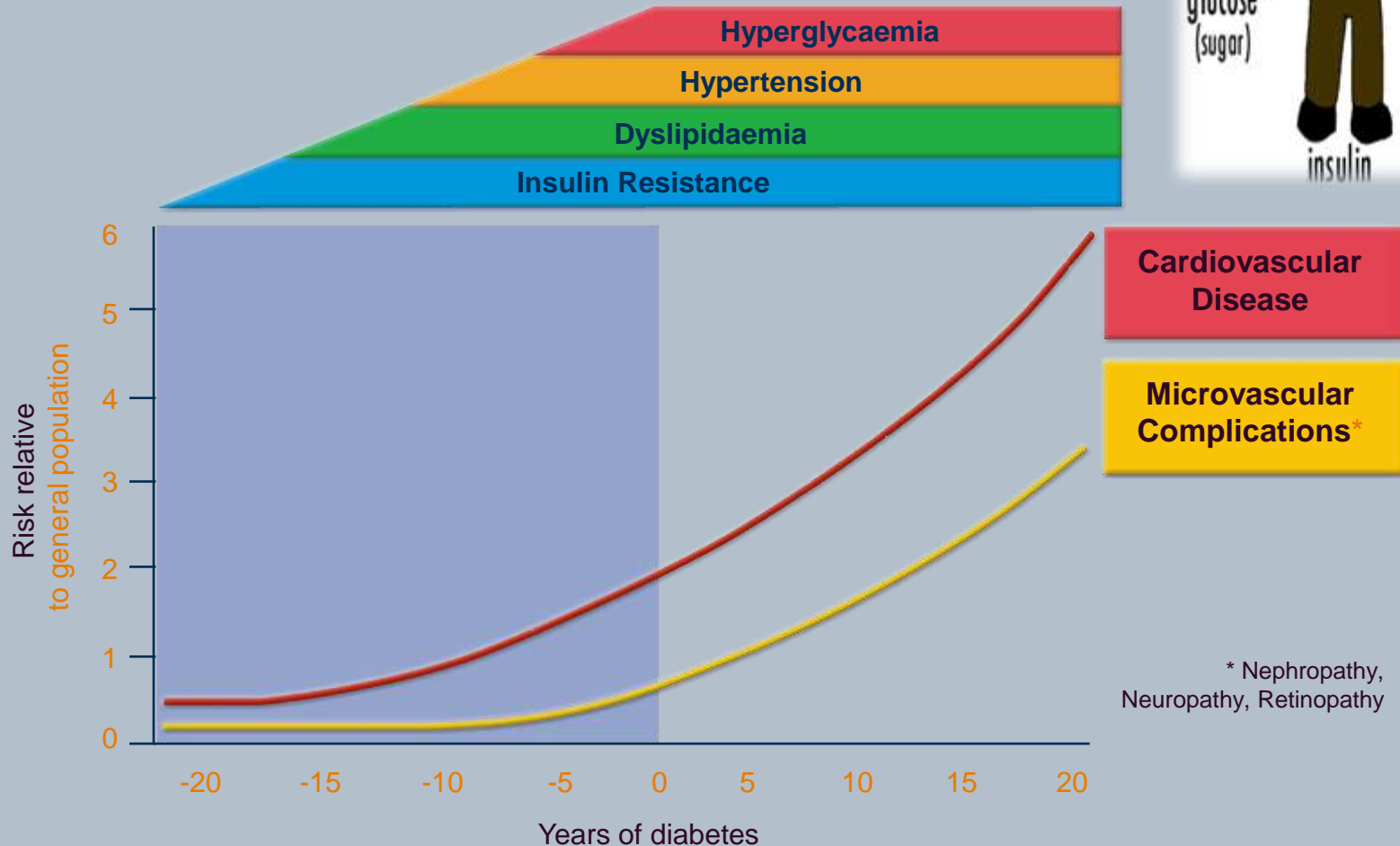


# Insulin resistance and $\beta$ -cell dysfunction are core defects of type 2 diabetes

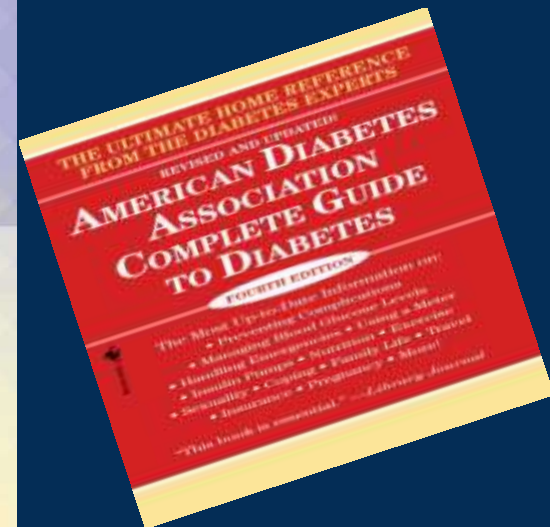
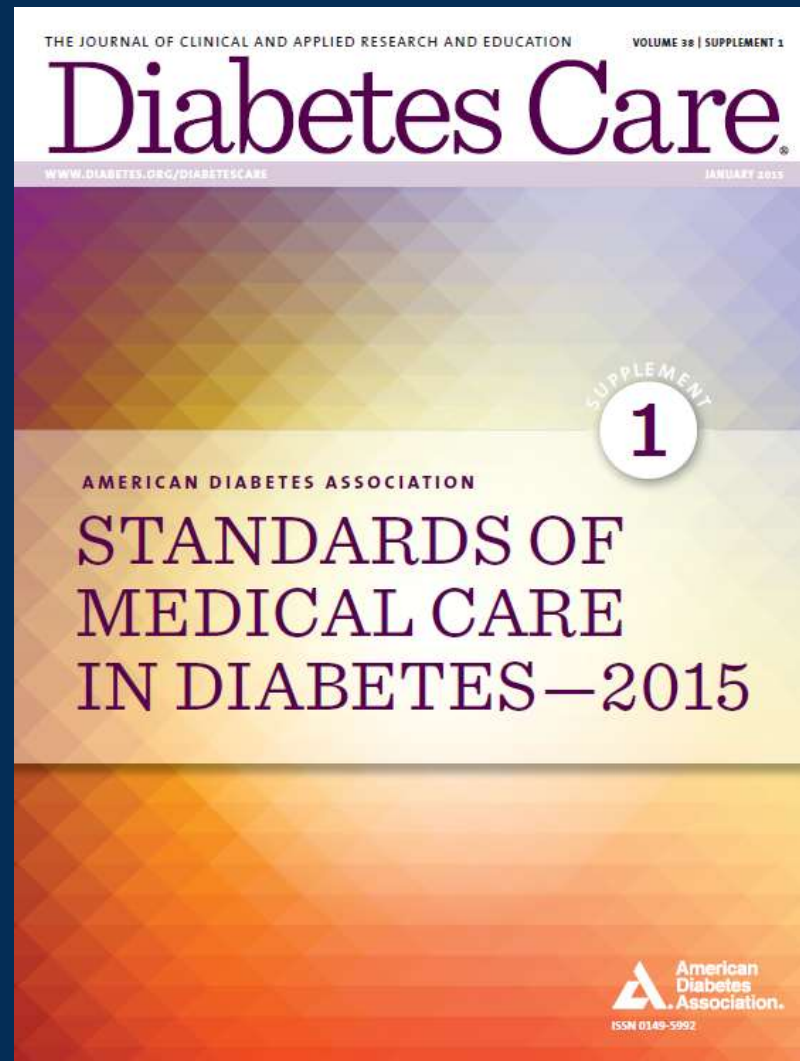




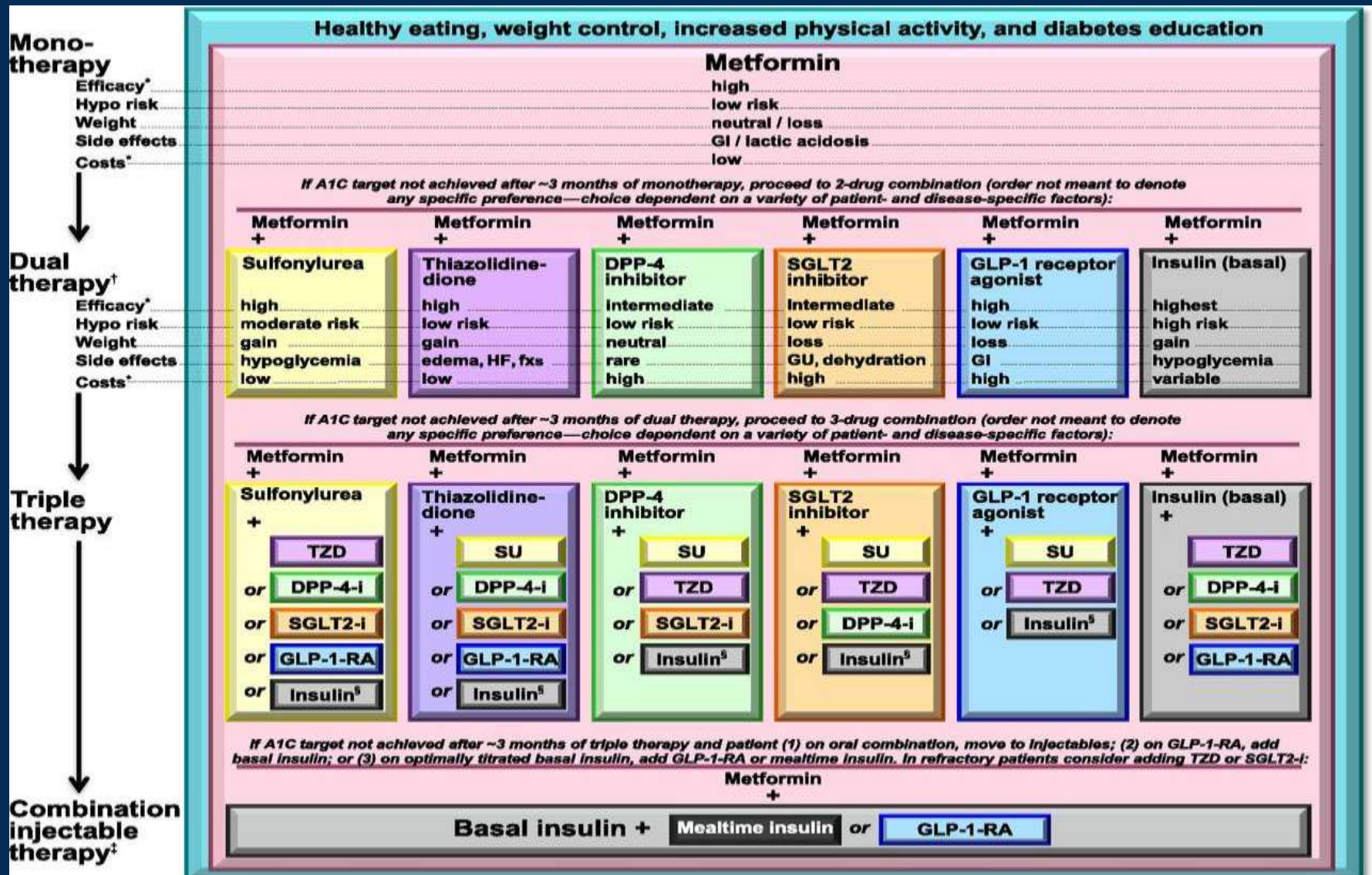
# Type 2 diabetes: Course of disease



# STANDARDS OF MEDICAL CARE IN DIABETES—2015

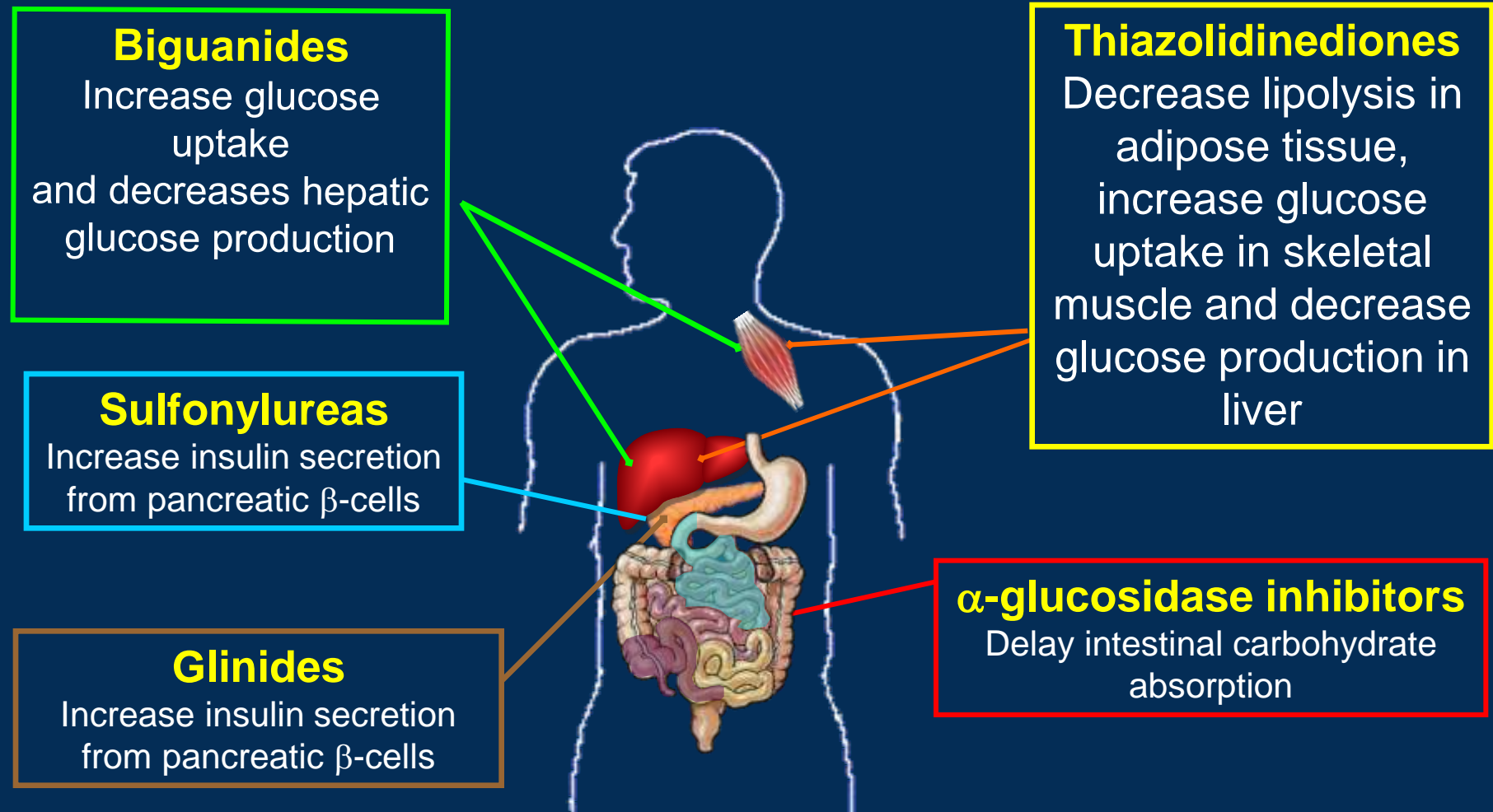


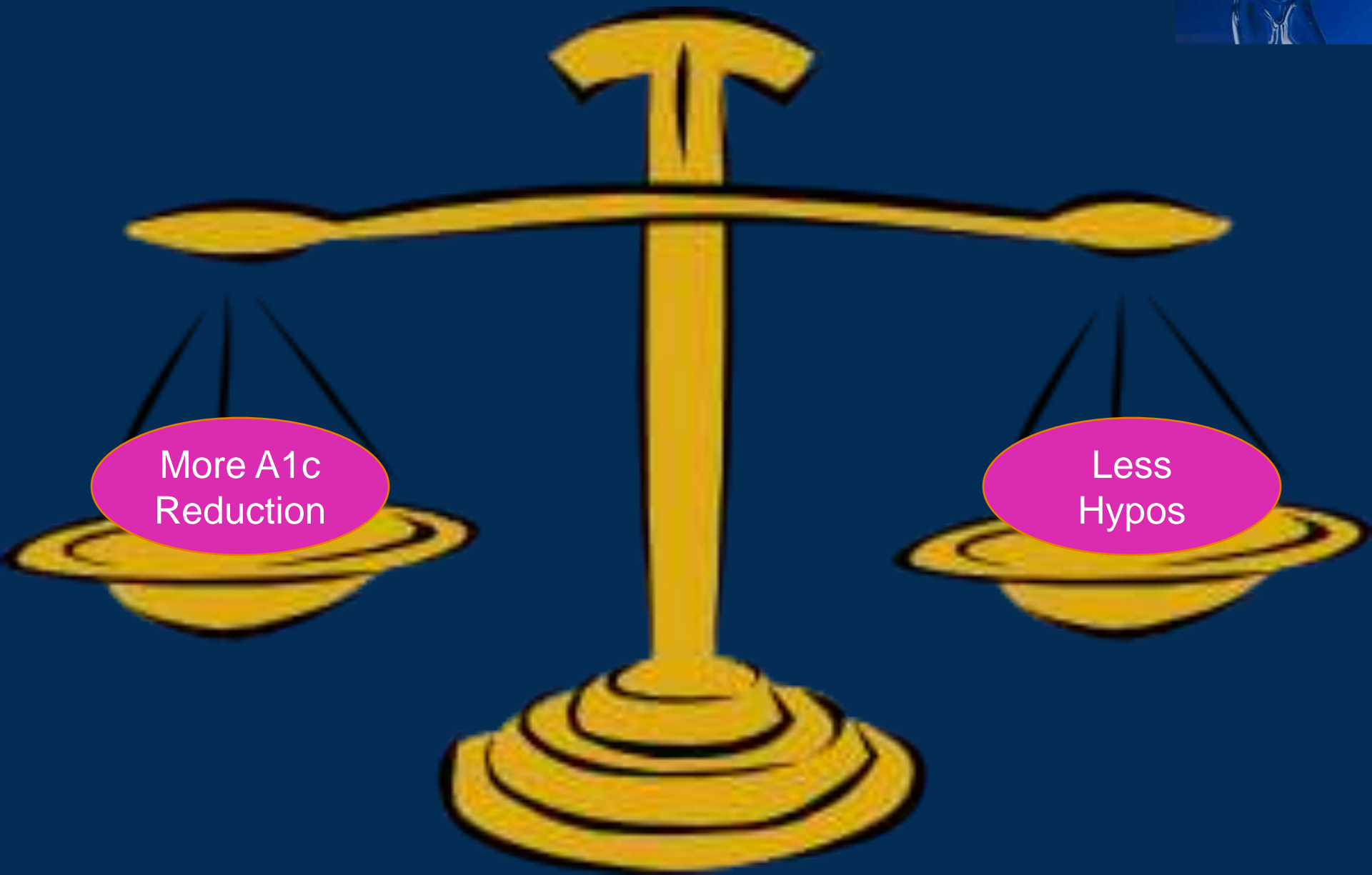
# Antihyperglycemic Therapy in Type 2 Diabetes





# Pharmacologic targets of current drugs used in the treatment of T2DM





More A1c  
Reduction

Less  
Hypos

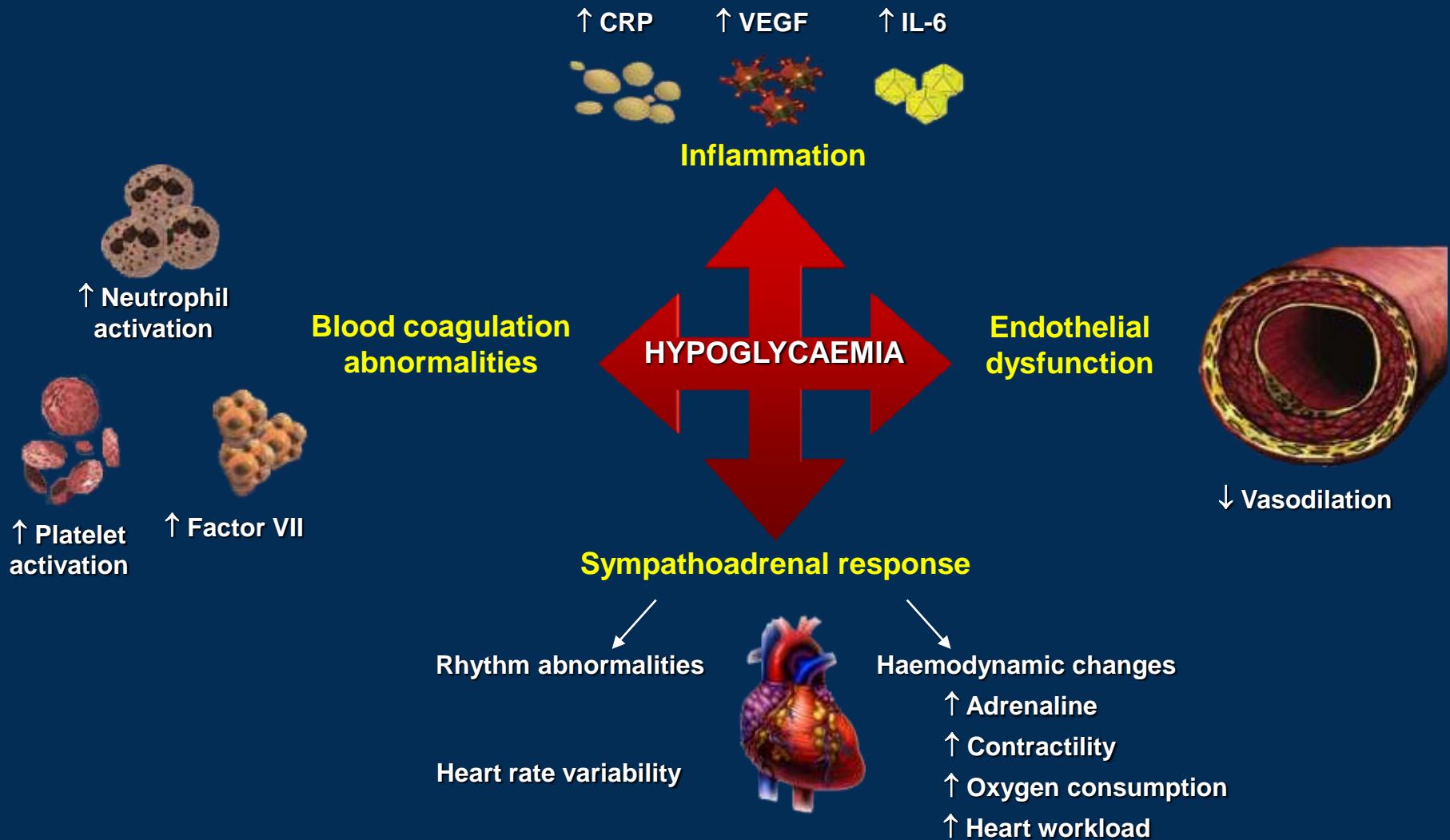


# What are the challenges in management of T2DM ?



1. Hypoglycemia
2. Glycemic Variations
3. Increased Cardiovascular Risk
4. All of the above
5. None of the above

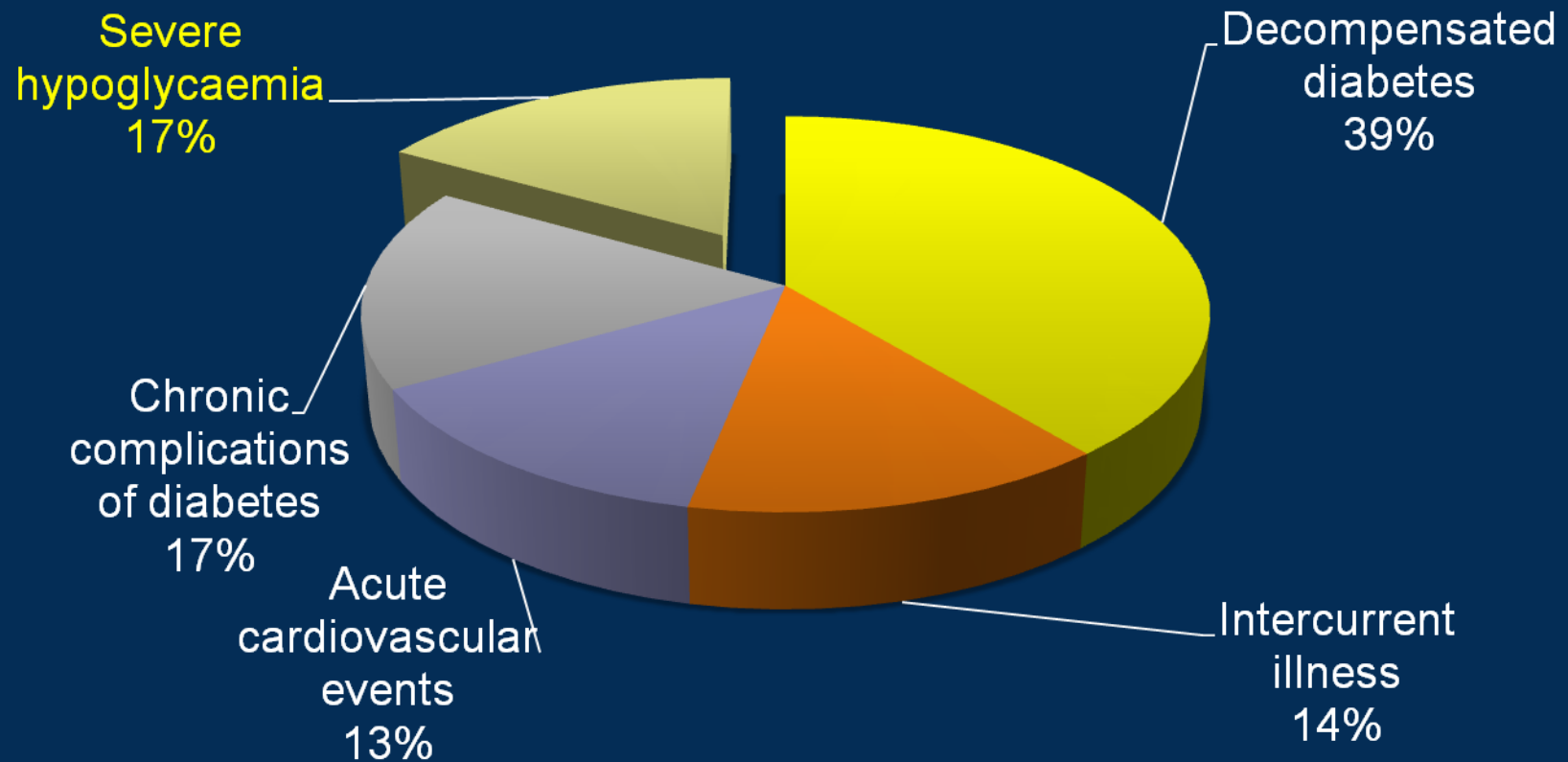
# Pathophysiological cardiovascular consequences of hypoglycaemia



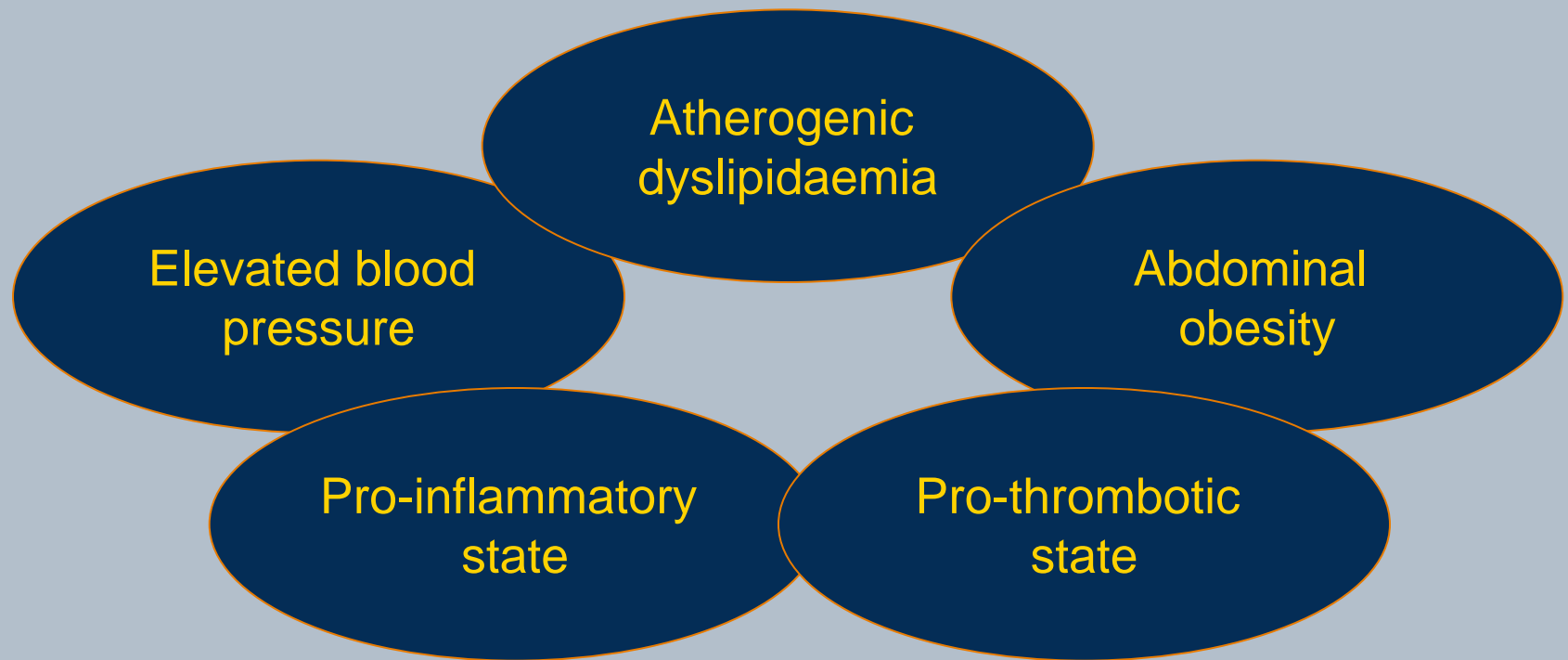
CRP=C-reactive protein; IL-6=interleukin 6; VEGF=vascular endothelial growth factor.  
Desouza CV, et al. *Diabetes Care*. 2010; 33: 1389–1394.

# Severe hypoglycemia is a concern with elderly

Severe hypoglycemia accounts for almost 20% of all hospitalizations for T2DM in the elderly



# Patients with or at risk of T2D often display a clustering of metabolic risk factors...



# Dietary changes prevent atherosclerosis

Dietary changes to prevent atherosclerosis include:

Substantial reduction of saturated fat

Switch saturated fats to unsaturated (preferably monounsaturated) fats and oils

Increasing consumption of fish

Increasing consumption of vegetables, fruit and whole grains



Mechanisms through which such dietary changes decrease CVD risk include:

Improved blood lipid profile

Decreased oxidation of lipids

Lowered risk for atherothrombosis (blood clot)

Improved endothelial function

Reduced insulin resistance



# Dyslipidaemia can be managed pharmacologically through monotherapy or combination therapy

## Monotherapy

- Statins
- Fibrates
- Bile acid sequestrants
- Nicotinic acid
- Intestinal cholesterol absorption inhibitors
- Other lipid altering agents:
  - CB1 antagonists
  - Omega 3

## Combination therapy

- Statin and fenofibrate
- Fenofibrate and ezetimibe
- Fibrate and nicotinic acid
- Statin and nicotinic acid
- Statin and ezetimibe
- Statin and fenofibrate and ezetimibe

**The secret to success is consistency to purpose**

**Benjamin Disraeli**



# Hypertension & Diabetes...Magnitude of problem

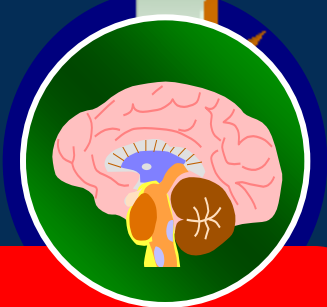
## Hypertension Represents a Significant Burden on Healthcare

- Worldwide, hypertension is responsible for
  - 62% of strokes<sup>1</sup>
  - 49% of heart attacks<sup>1</sup>
- Hypertension is the third leading risk factor for disease
  - Causes 7.1 million premature deaths each year<sup>1</sup>
  - 4.5% of global burden of disease<sup>1</sup>
- Hypertension represents a high burden on healthcare expenditure
  - In 2014, the direct and indirect cost of high blood pressure in the US was \$55.5 billion; drug costs accounted for \$21 billion<sup>2</sup>

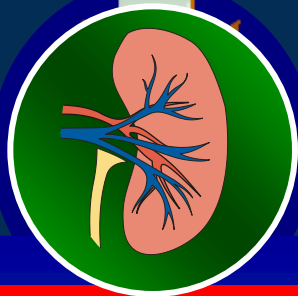
**Thus, hypertension management is a public health priority**

# Clinical Impact of Hypertension

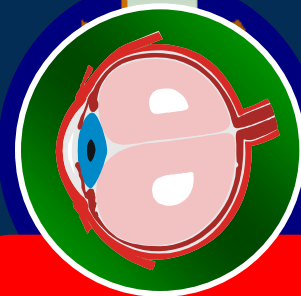
## Hypertension



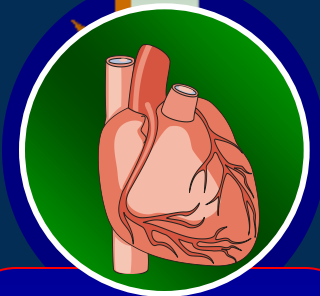
**2-4 fold increase  
in strokes**



**The 2<sup>nd</sup>  
leading  
cause of new  
cases of end  
stage renal  
disease**



**Contributes to  
visual loss in  
people with  
diabetes**



**Increased  
Death from  
MI and CHF**

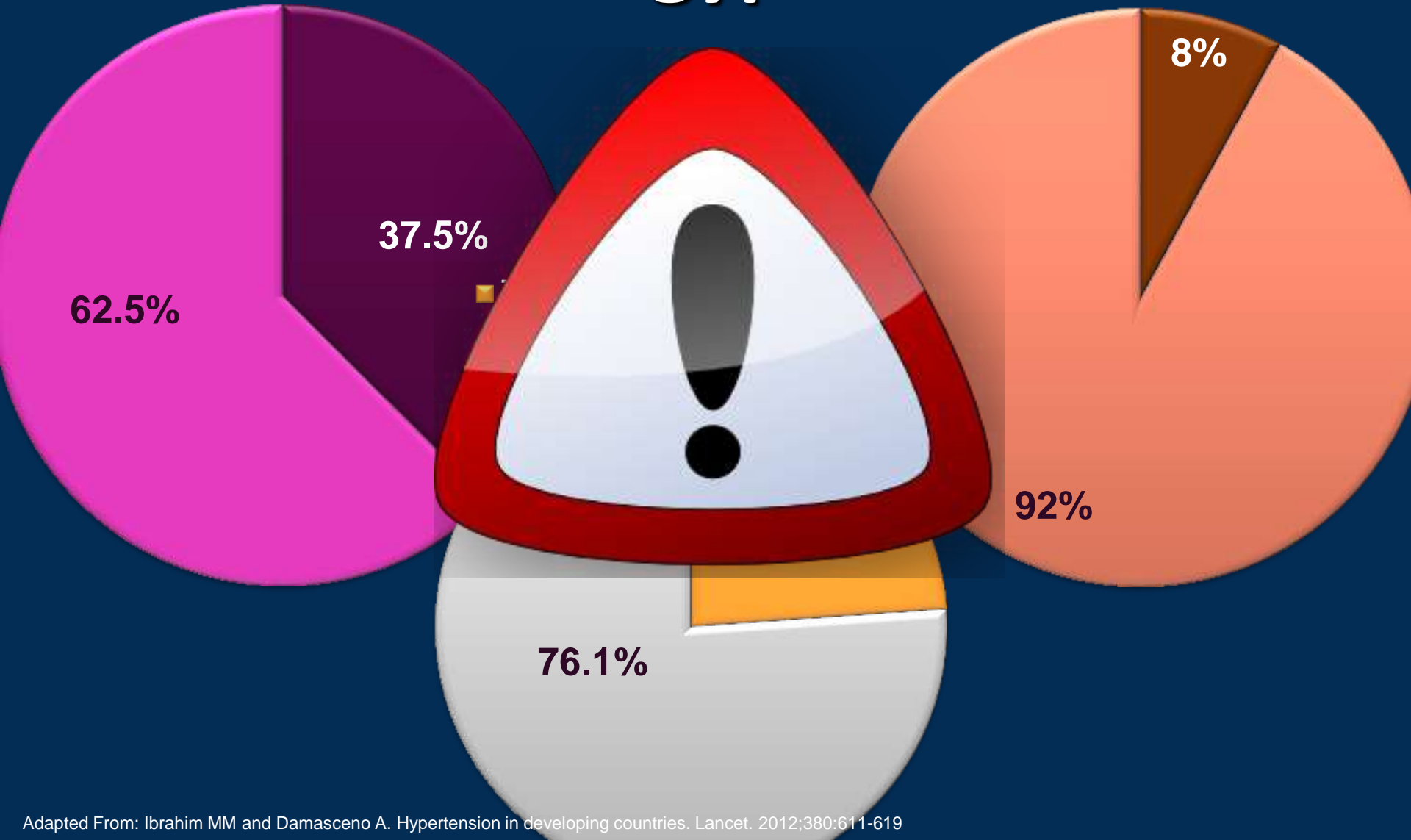
# Hypertension Control Rate in Egypt

■ Aware

■ Non-Aware

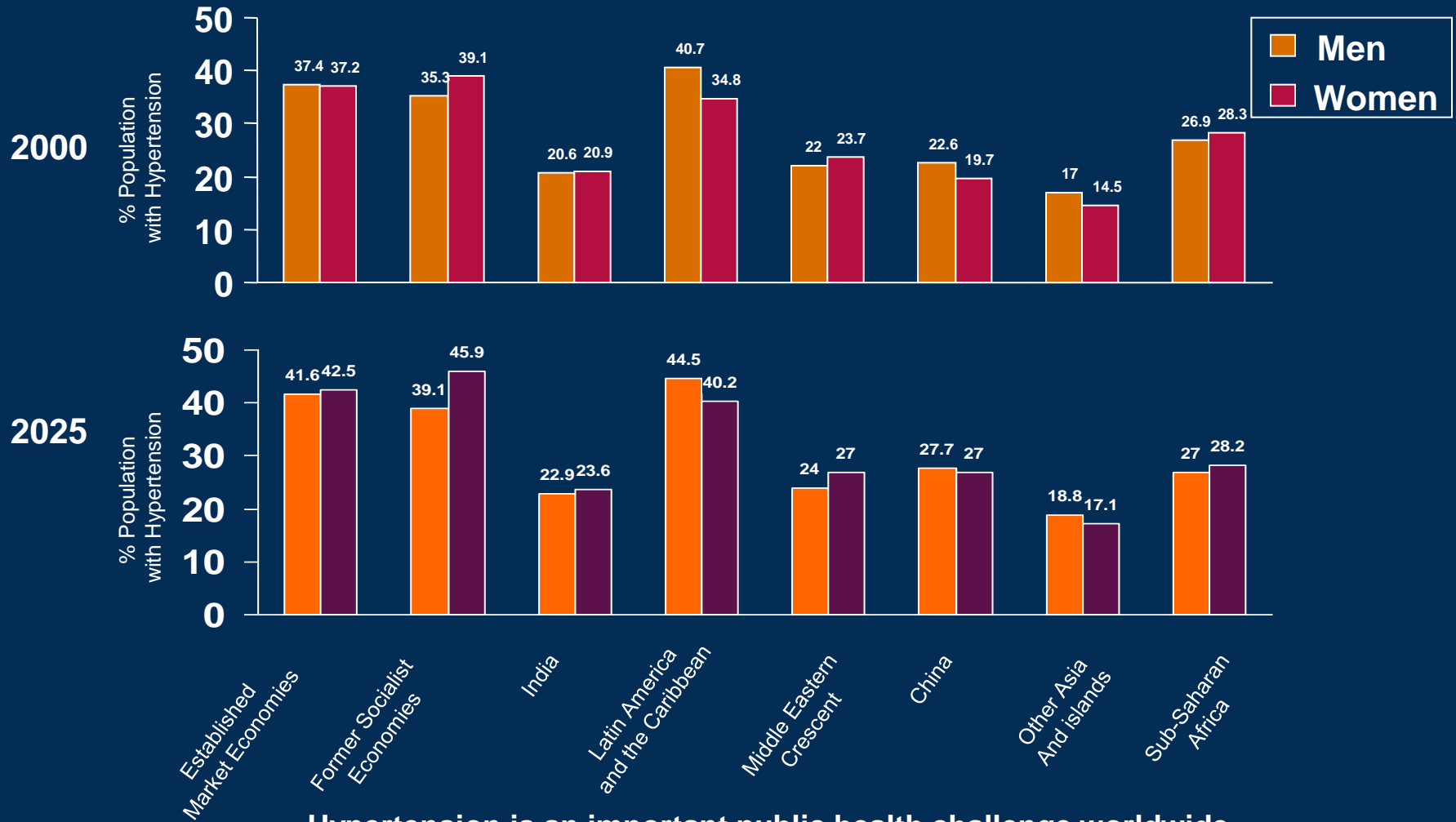
■ Controlled

■ Uncontrolled





# Hypertension Has a High Prevalence That Is Expected To Rise Over the Coming Decades...

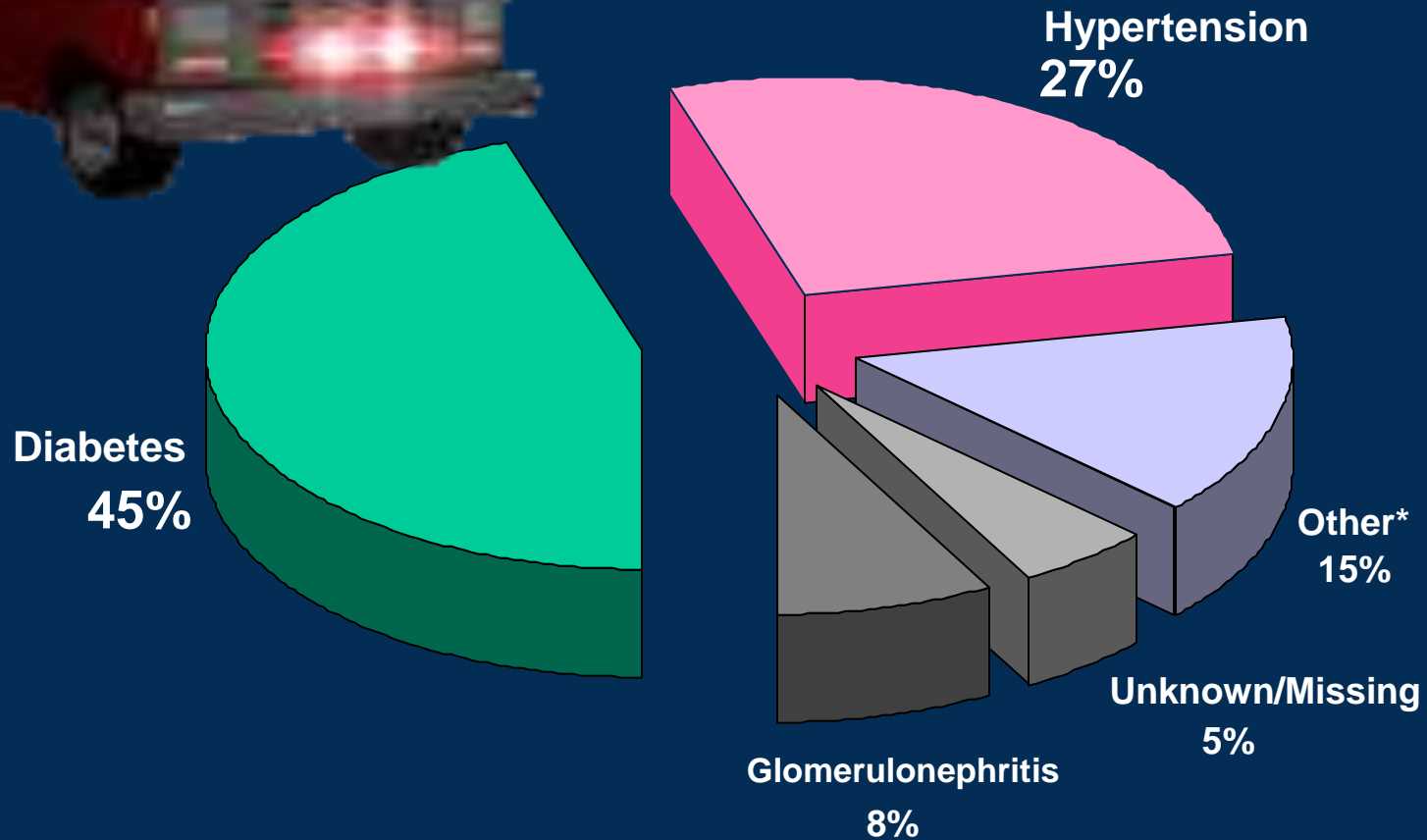


Hypertension is an important public health challenge worldwide. Prevention, detection, treatment and control should receive high priority

## Hypertension Often Coexists With Type 2 Diabetes and Reflects the Onset of Renal Disease

- The prevalence of hypertension in patients with diabetes is 1.5-2.0 times greater than in a matched nondiabetic population
- The prevalence of hypertension (BP >140/90 mmHg) among type 2 diabetics is:
  - 71% among those with normal albuminuria
  - 90% among those with microalbuminuria
- People with both diabetes and hypertension have approximately twice the risk of cardiovascular disease as non-diabetic people with hypertension
- The coexistence of hypertension and diabetes accelerates the progression of diabetic renal disease

# Hypertension and Diabetes Are Major Primary Diagnoses in Patients Who Start Dialysis for ESRD



# Management of Hypertensive Diabetics

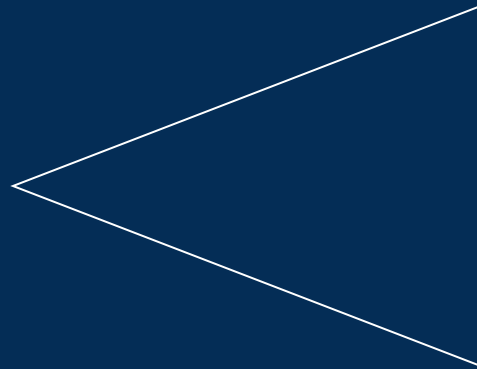
- Proper blood sugar control
- Early Detection of both diabetes and hypertension complications & manage them as well as delay their progression
- Improve patients quality of life (Encourage life style modification)

**Achieve target level of BP control**

# **BP Reductions as Little as 2 mm Hg Reduce the Risk of CV Events by Up to 10%**



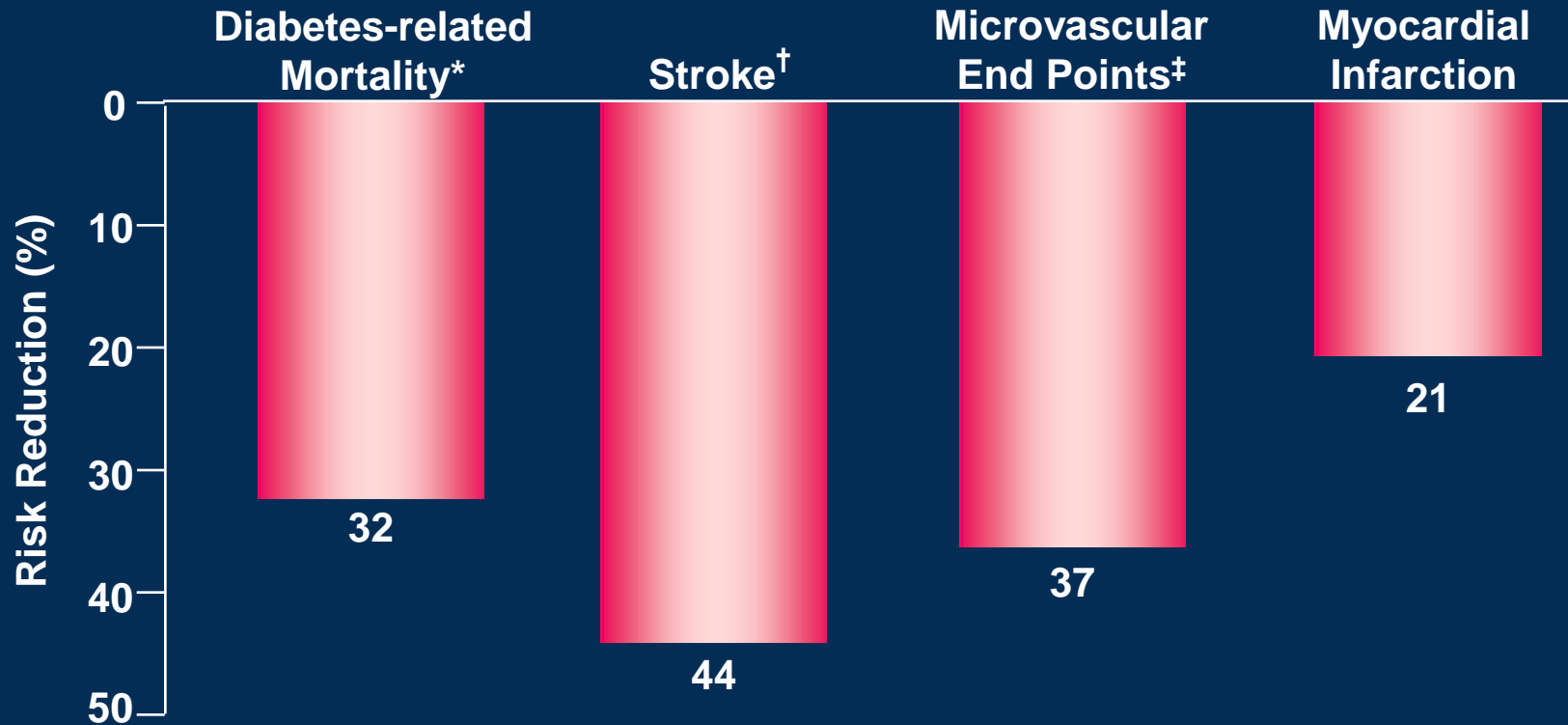
**2 mm Hg  
decrease in mean  
SBP**



**7% reduction in  
risk of ischemic  
heart disease  
mortality**

**10% reduction in  
risk of stroke  
mortality**

# Risk Reduction of Diabetes-Related End Points with Tight BP Control



\* Death due to MI, sudden death, stroke, peripheral vascular disease, renal disease, hyperglycemia, or hypoglycemia.

† Fatal or nonfatal.

‡ Retinopathy requiring photocoagulation, vitreous hemorrhage and fatal or nonfatal renal failure.



**In order to improve HTN control rate, we need to over-think a medication before we prescribe according to our habits**

**When to Titrate?**

**When to Add?**



# At Least 2 Are Required



God Sets Adam and Eve



Two Wheels To Move

adherence

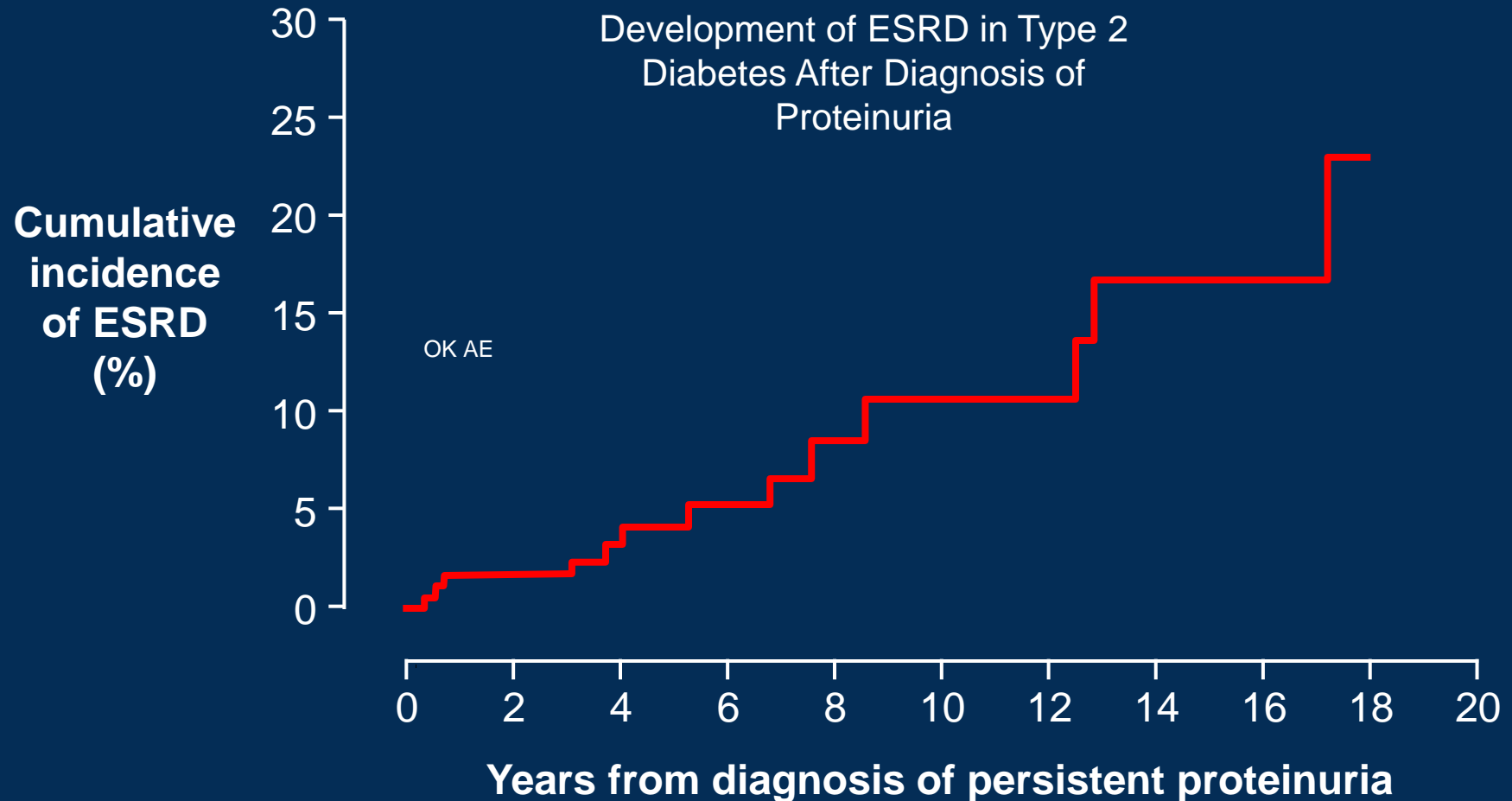


At Least 2 Drugs Are Required to Reach Blood Pressure Control

# Target Levels of Blood Pressure in Diabetic Patients

- Target blood pressure goal  $< 130/80$  mmHg
- Target blood pressure goal  $< 125/75$  mmHg if proteinuria  $> 0.5 - 1$  g/d is present

# Proteinuria is a predictor of the progression of renal disease in patients with Type 2 Diabetes



# Time to retire “Microalbuminuria”

Finding about TNFR1 and TNFR2 have a lot of translational potential.

1. Serum levels of these receptors are correlated and stable over time. Thus determination of TNFR1 or TNFR2 can predict the risk of early renal decline and ESRD during the subsequent 8-12 years.
2. These findings are being used to develop a clinical test to identify patients at high risk of early progressive renal decline and ESRD.



# Time to retire “Microalbuminuria”

Finding about TNFR1 and TNFR2 have a lot of translational potential.

3. The mechanism of these associations are unknown.
4. High circulating levels of TNFRs is a possible risk factor for early progressive renal decline.
5. Can lowering serum levels of TNFRs be a therapeutic target to postpone onset of ESRD in T1D and, possibly in T2D.

# **Time to retire “Microalbuminuria”**

- **Diabetic nephropathy remains an important health problem.**
- **Both albuminuria and GFR have strengths and limitations.**
- **Assessment of both allows for improved prognostication of renal and CV events in the general population and in diabetes.**
- **T1D patients with more serious underlying renal injury are at increased risk of renal progression.**
- **T2D patients with reduced GFR may have atypical DN lesions as well as other renal diseases.**

# **Time to retire “Microalbuminuria”**

**Current recommended screening tests (albuminuria and GFR) don't identify all patients with diabetic kidney disease since serious diabetic glomerular lesions can be present with normal GFR.**

# Time to retire “Microalbuminuria”

## Why do we need new markers?

- Albuminuria is not approved by FDA.
- Not all patients with albuminuria progress to ESRD.
- Prognosis of normoalbuminuria with CKD not clear.
- Recently albuminuria lowering trials have failed.
- Multiple disease driving pathways activated.
- Multiple markers could individualize treatment.

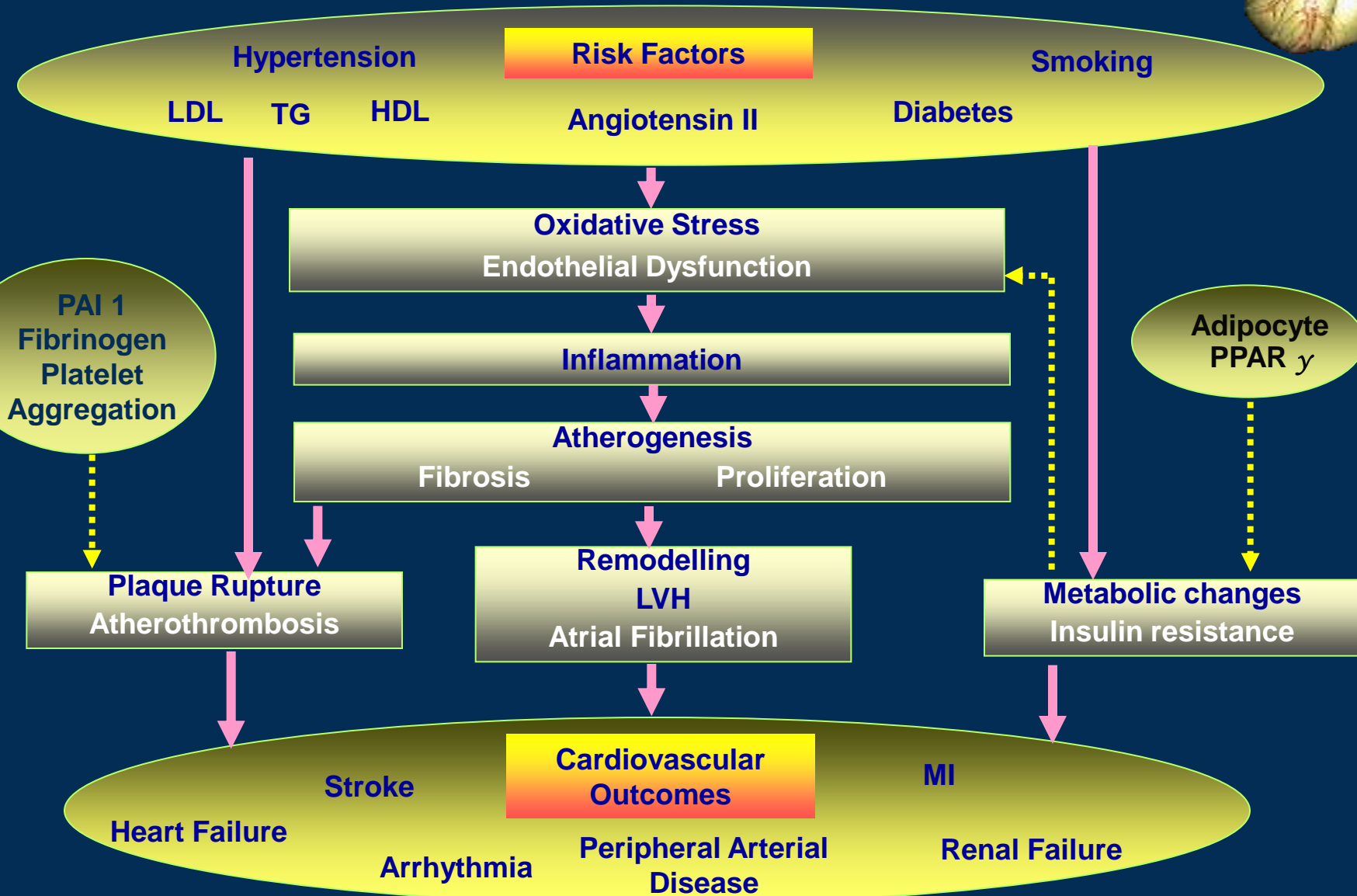
# **Time to retire “Microalbuminuria”**

## **Novel Markers**

- **Identifying patients at high risk for development of micro and macrovascular complications.**
- **Monitor progression of disease and treatment efficiency.**
- **May identify new treatment targets.**
- **Predict risk of adverse effects or treatment efficacy.**



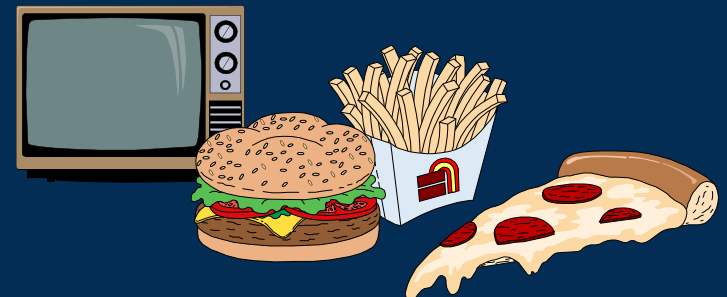
# Atherogenesis – origins and outcomes



Harrison D et al. *Am J Cardiol* 2003; 91(3A): 7A-11A; Munger MA et al. *J Am Pharm Assoc (Wash DC)* 2004; 44(2 Suppl 1): S5-12 3. Murtagh BM et al. *J Invasive Cardiol* 2004; 16(7): 377-384 4. Shishehbor MH et al. *Curr Atheroscler Rep* 2004; 6(3): 243-250

# Obesity Is Caused By Complex Interactions

## Genes Vs Changing lifestyle



# Role of Abdominal Adipocytes in Insulin Resistance and Heart Disease



**Abdominal  
Adipocytes**



**Adipocytokines + Fatty Acid**



**Insulin Resistance**



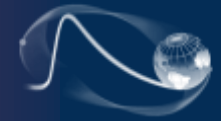
**Metabolic Syndrome**



**Heart Disease**



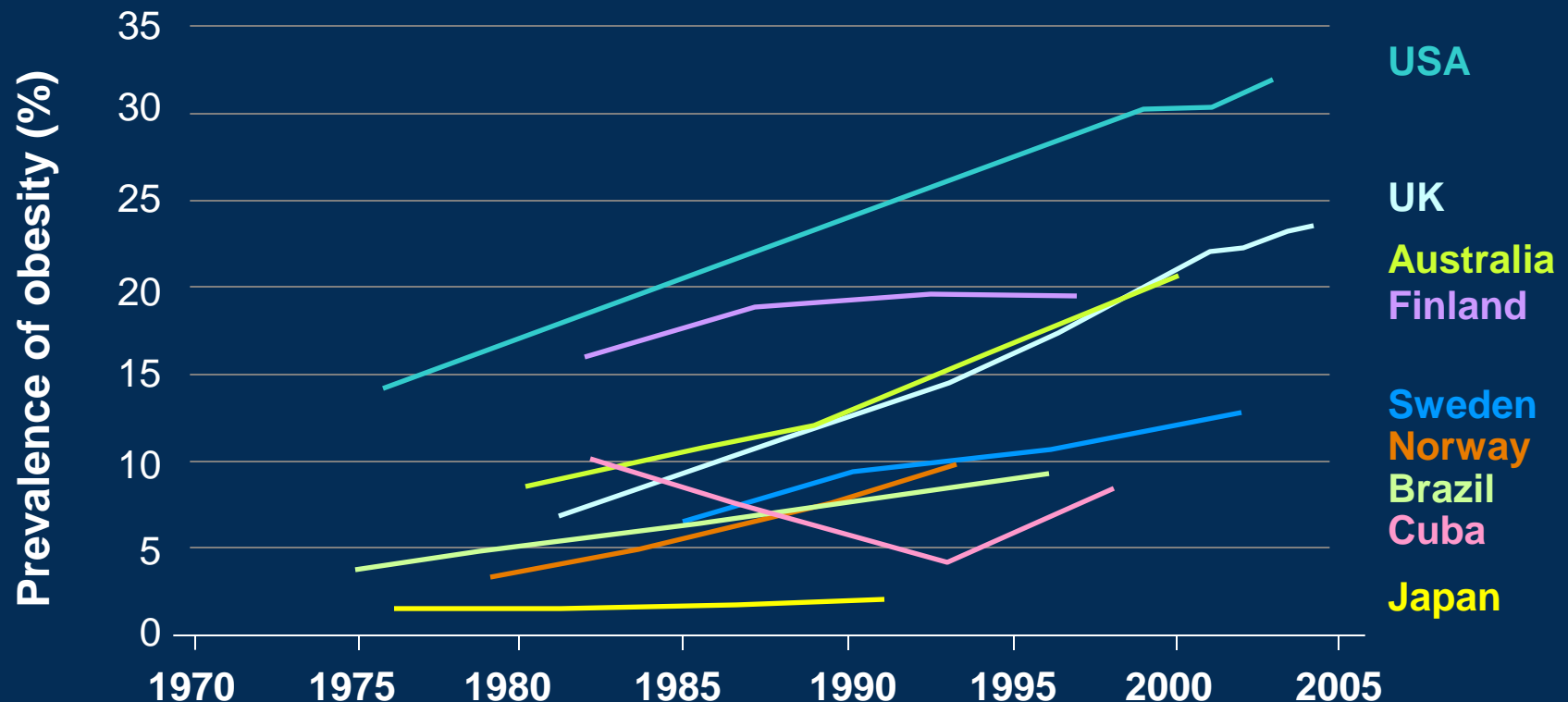
# Global Increase in Obesity



**WorldWIDE**

Worldwide Initiative for Diabetes Education

	2002	2007	2015
Obese	356 million	523 million	704 million
Overweight	1.4 billion	1.5 billion	2.3 billion



Overweight, BMI  $\geq 25$  kg/m<sup>2</sup>; obese, BMI  $> 28$  kg/m<sup>2</sup> (Asian) or  $> 30$  kg/m<sup>2</sup>.

James WP. *J Intern Med.* 2008;263:336-352.

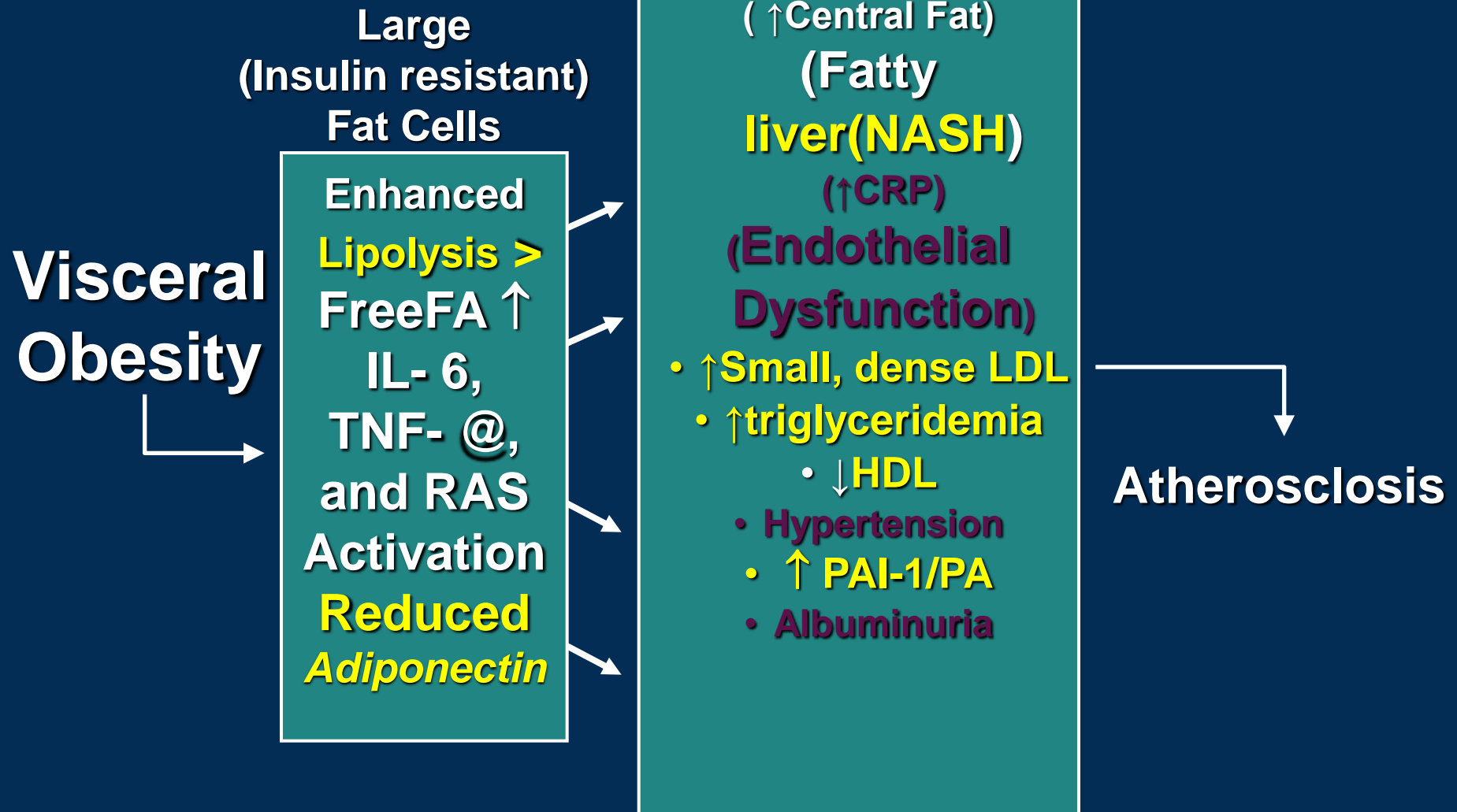
Like Mother

Like Daughter

HEALTH LEGACY SUMMIT



# Cardiometabolic Syndrome:





# Renal Factor

- In general population, obesity is associated with an increased incidence of chronic kidney disease and ESRD.
- The relationship between body mass index and impairment of renal function is evident even in subjects without overt obesity .
- On the other hand, in patients with established renal disease, obesity accelerates progression of renal damage.

# RENAL HEMODYNAMIC CHANGES

- **Obesity is associated with increased (RAAS) and (SNS) activity and hyperinsulinemia, all of which may contribute to sodium reabsorption and fluid retention.**
- **A compensatory lowered renal vascular resistance, elevated kidney plasma flow, increased glomerular filtration rate and higher BP, are mediated to overcome the increased sodium reabsorption.**

A photograph of a man from behind, walking on a paved area. He is wearing a white t-shirt with a graphic that says "LARGEMOUTH" above a large fish. He is also wearing light-colored shorts and sandals. The background shows other people and a building.

**An Obesity Tipping Point?**

# COMMENTS





# **Thank you for your attention**

Any questions?